Formation of Oxime and Isoxazoline from Aldehyde Derivatives via One-Pot Synthesis

An Honors Thesis (HONR 499)

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Abstract

Isoxazolines and isoxazoles are used as intermediates to create important functional groups. They also have practical uses such as the products soretolide, an epileptic seizure medication, valdecoxib, an anti-inflammatory drug, muscimol, a GABA receptor, and isoxaflutole, a pesticide. Finding a one-pot synthesis to produce isoxazoline from an aldehyde will be time and resource efficient. The one-pot synthesis then can be used for when doing a synthesis with an isoxazoline as an intermediate or just to make isoxazoline products. The most successful type of aldehyde used to make isoxazoline using one-pot synthesis is aromatic aldehydes without an alcohol group. The specific aldehydes that were tested are anisaldehyde, 3,4,5-trimethoxybenzaldehyde, and 3-nitrobenzaldehyde. The reactants used are hydroxylamine hydrochloride, 10% sodium hydroxide, ethanol, water, allyl alcohol, bleach, and dichloromethane. Aliphatic aldehydes like heptaldehyde and butrylaldehyde were also tested. The only change in the procedure when using aliphatic aldehydes is using 50% sodium hydroxide instead of 10% sodium hydroxide. Even though this procedure would make isoxazoline, there was a large amount of impurities with little isoxazoline. Further research would need to be done to find a better procedure to make more isoxazoline.

Acknowledgments

I would like to thank Dr. Robert Sammelson for allowing me to be a part of his research group and being my advisor throughout this project. He was always willing to guide me to the right direction and give me any help I needed. I would like to also thank everyone in the Sammelson Research Group. Many of them helped me discuss ideas and came up with solutions to problems. Lastly I want to thank Komal Kumar and Terry Park. These two academy students help get the project started.

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Process Analysis Statement

I joined Dr. Sammelson's lab in the summer of 2019. Dr. Sammelson's lab focuses on areas of synthetic methods and organic compounds with medicinal and bioorganic applications. Many members in the laboratory are investigating compounds that possess nitrogen containing heterocycles.

My research involves studying oxime and isoxazolines reactions and finding a way to make isoxazoline in one-pot. I want to find one-pot reactions because it is more efficient to do all steps in one flask rather than extracting the product after each step. In a typical synthesis, I would make oxime from aldehyde and then isoxazoline from oxime. In a one-pot reaction, I would start with aldehyde and directly make isoxazoline. Doing a one-pot reaction takes less time and less reactants which for a company would save money. I am researching isoxazolines and isoxazoles because they are used to make helpful functional groups, like 3-hydroxybutanoic acid, and have practical applications, like medical drugs. Since so many reactions can be done with isoxazolines and isoxazoles, finding a more efficient way to make isoxazolines and isoxazoles is favorable.

Most of the instruments and techniques I used during this research was learned while I took Organic Chemistry 1 and 2. Even though I knew how to perform extractions and use a rotovap and NMR, I was able to perfect my skills. The greatest skills I learned during this research is how to problem solve and think critically. When I was in Organic Chemistry lab, the reactions are meant to work. During research, this is not always true. Many times I would do reactions and they would not work. Even

sometimes I would do the same reaction twice and it would only work once. For example, the first time I tried to make isoxazoline from oxime, the reaction worked only once and the other three times it did not. Instead of just tossing the reaction aside, I tested what caused the reaction to not work. The reaction consistently made isoxazoline when I used pure oxime found in the laboratory instead of the oxime I made. The oxime I made was not pure and had small amounts of reactants in it. This told me that one of the reactants from the aldehyde to oxime procedure caused the isoxazoline procedure to not work. I did the oxime to isoxazoline reaction again but this time I added in 1 of the 3 reactants from the aldehyde to oxime procedure. I did this 2 more times with the other 2 reactants. I found that hydroxylamine hydrochloride was effecting the oxime to isoxazoline reaction from reacting. I was then able to research different reactions on databases and find an aldehyde to oxime procedure with less hydroxylamine hydrochloride. Critically thinking and experimenting allowed me to know why a reaction was not working. I was able to better estimate which reactions would work instead of blindly trying new reactions. These skills are something I did not learn in class and are very important to know as a research chemist.

Introduction

The purpose of this research is to test the reaction limits of oxime, isoxazoline, and isoxazoles and to find a more efficient way to produce them through one-pot synthesis. Isoxazolines are used as an intermediate to make important functional groups so finding ways to synthesize them efficiently can be very helpful. **Figure 1.1** shows many pathways from the literature.[1]

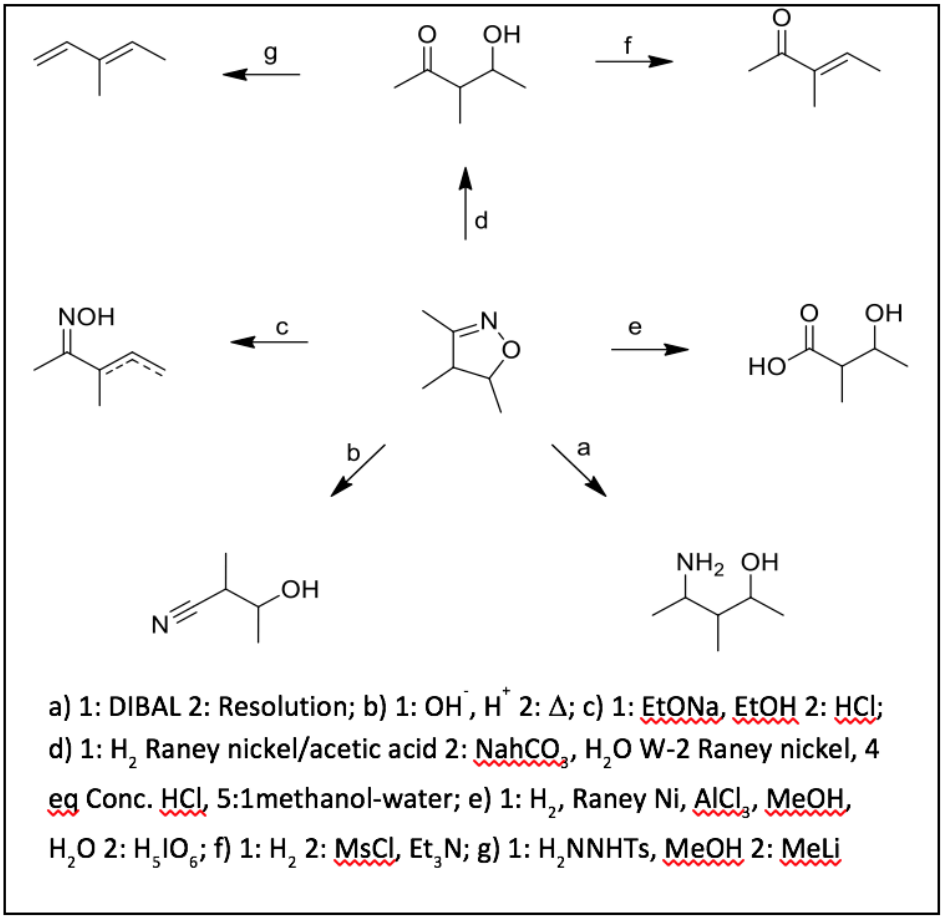


Figure 1.1 Synthetic Pathways of Isoxazoline

Also finding effective ways to synthesize isoxazoles is beneficial because isoxazoles are used in many practical products such as Soretolide, Valdecoxib, Muscimol, and Isoxazflutole. Soretolide is used as a treatment for epileptic seizures,[2] Valdecoxib is an anti-inflammatory drug,[3] Muscimal is a GABA receptor,[4] and Isoxaflutole is used as a pesticide.[5] Structures are shown in **Figure 1.2**.

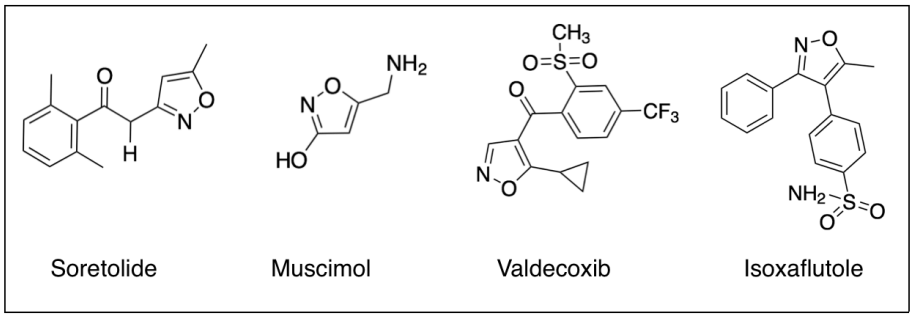


Figure 1.2 Structures of Practical Isoxazoles

As shown in **Figure 1.3**, to get the desired product the reaction starts with an aldehyde. This research will explore various different aldehydes and how that effects the intermediate, oxime, and the product, isoxazoline or isoxazole. Many different procedures and reactants will be tested to find a procedure to create the product in one-pot. **Figure 1.4** shows the mechanism of how aldehyde reacts to turn into oxime and then how oxime turns into isoxazoline. Knowing the reaction mechanism is important so if any side reactions happen during the reaction, it can be analyzed where during the reaction it occurred.

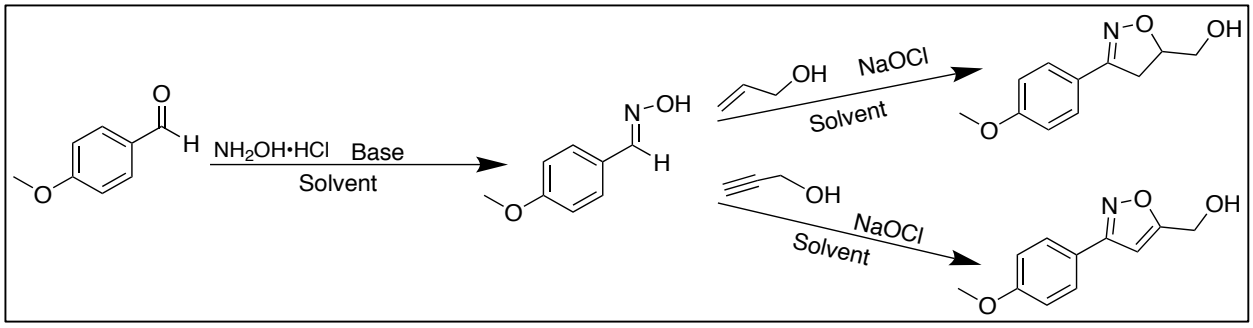


Figure 1.3 Synthesis of Isoxazoline Main Reaction

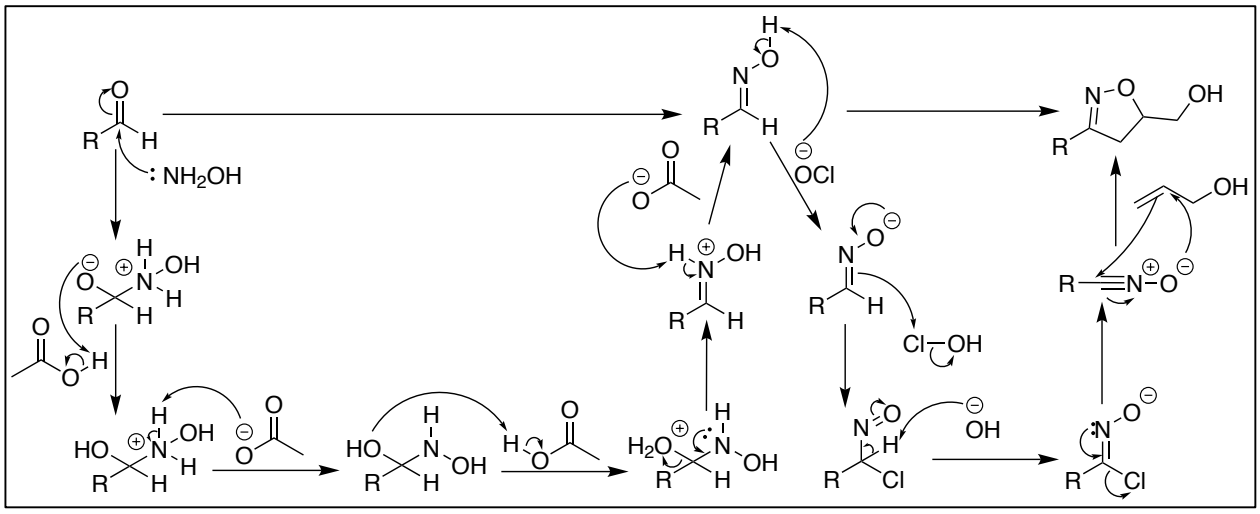
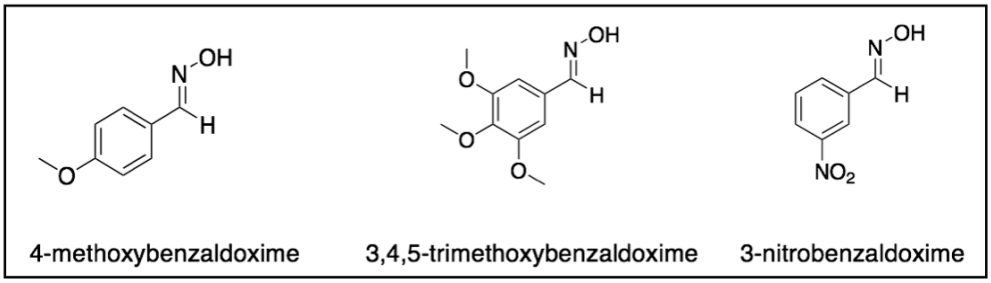


Figure 1.4 Reaction Mechanism

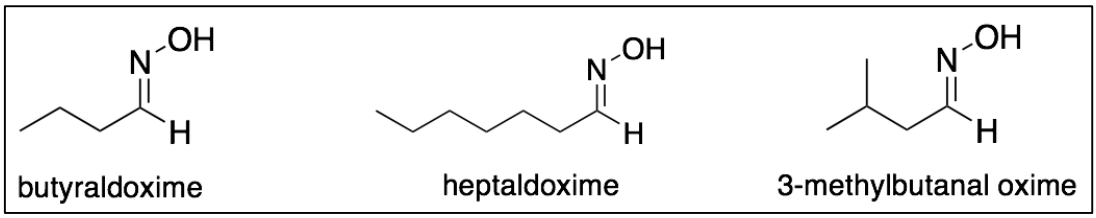
Experimental

Figure 1.5 Oximes Synthesized from Aromatic Aldehydes



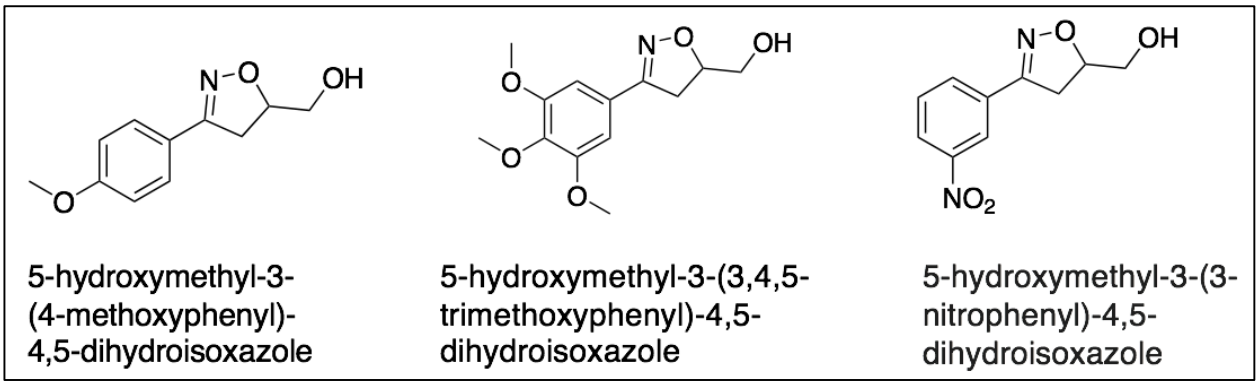
A solution of 10% (w/w) sodium hydroxide solution was made. In 50mL round-bottom flask, hydroxylamine hydrochloride (0.0834 g, 1.2 mmol) was weighed. Into the flask, water (0.7 mL) was added. In a graduated cylinder, 10% sodium hydroxide (0.5 mL) was measured and added into the round-bottom flask. In a separate beaker, aldehyde (1.0 mmol) is weighed and ethanol (3 mL) is measured and added into the beaker. A stir bar was placed in round-bottom flask and started stirring. While stirring, solution in beaker is added in the round-bottom flask dropwise. The flask was left stirring for 30-120 minutes. Once finished stirring, dichloromethane is used to extract the organic layer 2-3 times. Anhydrous magnesium sulfate was used as a drying agent and the solution was filtered into a tared round-bottom flask. Solution was then rotovapped and NMR spectra was obtained the remaining oil or crystals.

Figure 1.6 Oximes Synthesized from Aliphatic Aldehydes



A solution of 50% (w/w) sodium hydroxide solution was made. Hydroxylamine hydrochloride (0.0834 g, 1.2 mmol) was weighed into a 50mL round-bottom flask and then water (0.7 mL) was added. In a graduated cylinder, 50% sodium hydroxide (0.5 mL) was measured and added into the round-bottom flask. In a separate beaker, aldehyde (1.0 mmol) is weighed and ethanol (3 mL) is measured and added into the beaker. A stir bar was placed in round-bottom flask and started stirring. While stirring, solution in beaker is added in the round-bottom flask dropwise. The flask was left stirring for 30-120 minutes. After stirring, 1M HCl was added until pH is below 6. Ethyl Acetate is used to extract the organic layer 2-3 times. Anhydrous magnesium sulfate was used as a drying agent and the solution was filtered into a tared round-bottom flask. The solution was rotovapped to remove organic solvent and NMR spectra was obtained on the remaining oil or crystals.

Figure 1.7 Formation of Isoxazolines from Aromatic Oximes



Oxime (1.0 mmol) was weighed and placed in a 50mL round-bottomed flask. Allyl alcohol (0.116 g, 2.0 mmol) was weighed in a separate beaker and added into the round-bottom flask. A stir bar was added into the round-bottom flask and solution was stirred in an ice bath. DCM (7 mL) is measured in a graduate cylinder and added into round-bottom flask. A 3% bleach solution (4.96 g, 2.0 mmol) was added dropwise into the flask over 20-30 minutes. The ice bath was removed and solution was stirred for 30 minutes. The organic layer was extracted using dichloromethane. The solution was dried using anhydrous magnesium sulfate and then filtered into a tared round-bottom flask. The solution is then rotovapped and NMR spectra was obtained on the oil or crystal.

One-Pot Synthesis of Isoxazoline Starting with Aromatic Aldehyde

A solution of 10% (w/w) sodium hydroxide solution was made. In 50mL round-bottom flask, hydroxylamine hydrochloride (0.0834 g, 1.2 mmol) was weighed. Into the flask, water (0.7 mL) was added. In a graduated cylinder, 10% sodium hydroxide (0.5 mL) was measured and added into the round-bottom flask. In a separate beaker,

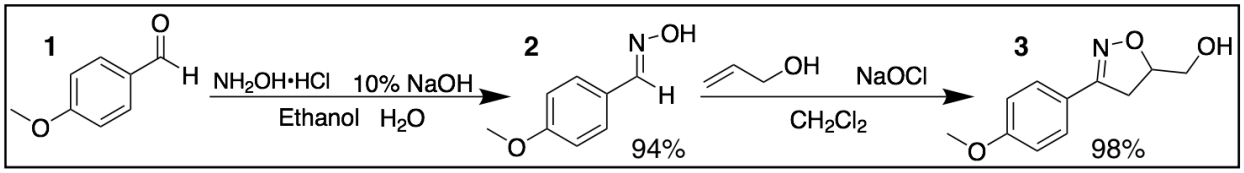
aldehyde (1.0 mmol) is weighed and ethanol (3 mL) is measured and added into the beaker. A stir bar was placed in round-bottom flask and started stirring. While stirring, solution in beaker is added in the round-bottom flask dropwise. The flask was left stirring for 30-120 minutes. Allyl alcohol (0.116 g, 2.0 mmol) was weighed in a separate beaker and added into the round-bottom flask. A stir bar was added into the round-bottom flask and solution was stirred in an ice bath. Dichloromethane (7 mL) is measured in a graduate cylinder and added into round-bottom flask. A 3% bleach solution (4.96 g, 2.0 mmol) was weighed and added in dropwise into the flask over 30 minutes. The ice bath was then removed and solution was stirred for an additional 30 minutes. Once solution was done stirring, the organic layer was extracted using DCM. The solution was dried using magnesium sulfate and then filtered into a tared round-bottom flask. The solution is then rotovapped and NMR spectra was obtained on the oil or crystals.

Results and Discussion

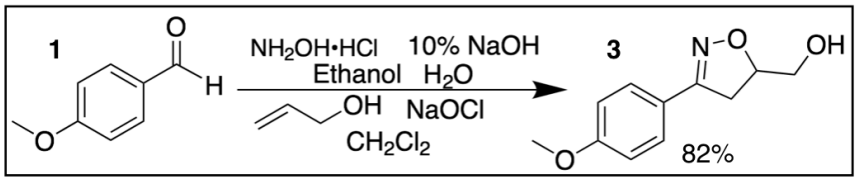
One-Pot Synthesis Starting with Anisaldehyde

Anisaldehyde (**1**) was the first aldehyde tested to find the best procedure to make oxime. Bases such as sodium acetate, sodium bicarbonate, and sodium hydroxide were tested. Many different equivalents of hydroxylamine hydrochloride and various ratios of the solvents water and ethanol were also tested. Reactions to form oxime (**2**) from aldehyde are already known reactions so many of these procedures created oxime. The next step is to create isoxazoline from oxime. Sodium hypochlorite (bleach), allyl alcohol, and dichloromethane were the reagents used. When using the oximes (**2**) from various procedures, most of the reactions did not produced the desired product, isoxazoline (**3**). This resulted in testing each reagent used in forming oxime to see if one does not allow the reaction to go to completion. The results of this shows that excess hydroxylamine hydrochloride does not allow the reaction to proceed forward to create isoxazoline (**3**). This information means less hydroxylamine hydrochloride needs to be use so there is not any leftover in the oxime. After finding a procedure with less hydroxylamine hydrochloride, oxime (**2**) was made and isoxazoline (**3**) reaction was finally able to go to completion. Once each step of the synthesis was successfully done, one-pot synthesis was tested starting with anisaldehyde (**1**) and ending with isoxazoline (**3**). Below **Scheme 1.1** and **Scheme 1.2** shows the reaction scheme and the percent yield of the product. Refer to **Spectrum 1.1**, **Spectrum 1.2**, and **Spectrum 1.3** in the Appendix for ^{1}H NMR spectra data to confirm products were made. In **Spectrum 1.1**, the desired product peaks are at 4.8 ppm, 6.9 ppm, 7.5 ppm, and 8.1 ppm. This

spectrum is very pure with only traces of impurities. **Spectrum 1.2** and **Spectrum 1.3** shows product peaks at 1.92 ppm, 3.24 ppm, 3.35 ppm, 3.65 ppm, 3.85 ppm, 4.84 ppm, 6.89 ppm, and 7.60 ppm. There are very trace amounts of aldehyde left at 9.87 ppm and there is quite a lot of water in at 1.56 ppm. The characterization of 5-hydroxymethyl-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (**5**) is as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 4.84 (m, 1H), 3.85 (m, 1H), 3.65 (m, 1H), 3.35 (dd, J = 15.7, 7.8 Hz, 1H), 3.24 (dd, J = 15.7, 7.8 Hz, 1H), 1.92 (br. t, J = 14.3 Hz, 1H).



Scheme 1.1 Synthesis of Isoxazoline starting with Anisaldehyde



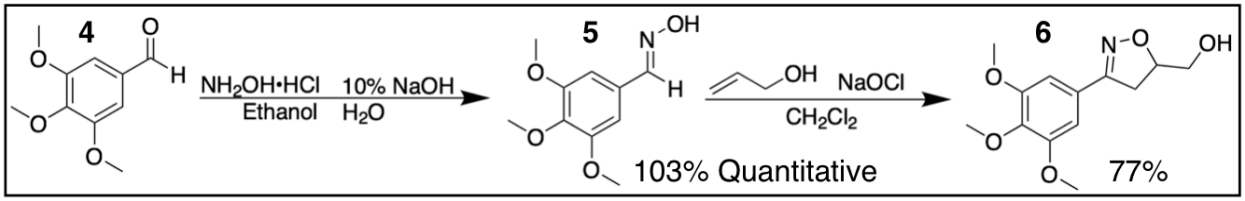
Scheme 1.2 One-Pot Synthesis Starting with Anisaldehyde

One-Pot Synthesis Starting with 3,4,5-Trimethoxybenzaldehyde and 3-Nitrobenzaldehyde

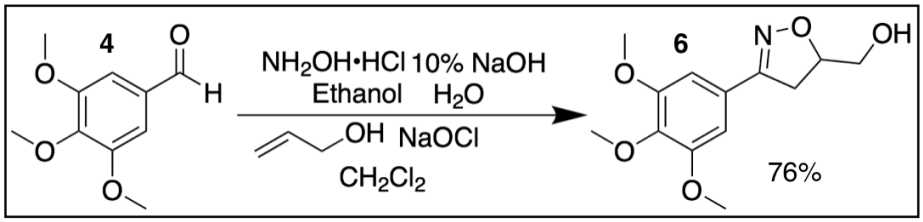
Various aromatic aldehydes were tested to see if the one-pot reaction done with anisaldehyde would work as well. The aromatic aldehydes tested were 3,4,5-trimethoxybenzaldehyde (**4**), 3-nitrobenzaldehyde (**7**), 3-ethoxy-2-

hydroxybenzaldehyde, 4-ethoxy-3-hydroxybenzaldehyde, and 2-hydroxy-1-naphthaldehyde. All these aldehydes successfully made oxime (**5**, **8**) while only 3,4,5-trimethoxybenzaldehyde and 3-nitrobenzaldehyde were able to form isoxazoline (**6**, **9**). It is speculated that the phenolic OH groups have a side reaction with the bleach or 1,3-dipolar cycloaddition and this is most likely why those 3 aldehydes could not react to produce isoxazolines. Further research would have to be done by installing a blocking or protecting group. A one-pot synthesis was successfully done starting with 3,4,5-trimethoxybenzaldehyde (**4**) or 3-nitrobenzaldehyde (**7**) to make isoxazoline (**6**, **9**). Below **Scheme 1.3**, **Scheme 1.4**, **Scheme 1.5**, **and Scheme 1.6** shows the reaction scheme and the percent yield of successful reactions. Refer to **Spectrum 1.4**, **Spectrum 1.5**, **Spectrum 1.6**, **Spectrum 1.7**, **Spectrum 1.8**, **and Spectrum 1.9** in the Appendix for ^{1}H NMR spectra. In **Spectrum 1.4**, the oxime peaks are at 3.85 ppm, 6.80 ppm, and 8.05 ppm. There are very little impurities which may only be water at 1.76 ppm. **Spectrum 1.5** and **Spectrum 1.6** has isoxazoline peaks at 2.06 ppm, 3.24 ppm, 3.35 ppm, 3.65 ppm, 3.85 ppm, 4.85 ppm, and 6.88 ppm. There is some excess DCM shown at 5.27 ppm which can be taken away by rotovapping longer. There is also water present at 1.65 ppm. The characterization of 3,4,5-Trimethoxybenzaldehyde is as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 2H), 4.84 (m, 1H), 3.85 (m, 1H), 3.65 (m, 1H), 3.35 (dd, J = 15.7, 7.8 Hz, 1H), 3.24 (dd, J = 15.7, 7.8 Hz, 1H), 2.06 (br. s, 1H). **Spectrum 1.7** shows oxime peaks at 7.56ppm, 7.70 ppm, 7.90 ppm, 8.21 ppm, and 8.44 ppm. **Spectrum 1.8** and **Spectrum 1.9** shows product peaks at 2.91ppm, 3.24 ppm, 3.35ppm, 4.95 ppm, 7.56 ppm, 8.04 ppm, 8.26 ppm, and 8.43 ppm. **Spectrum 1.9**

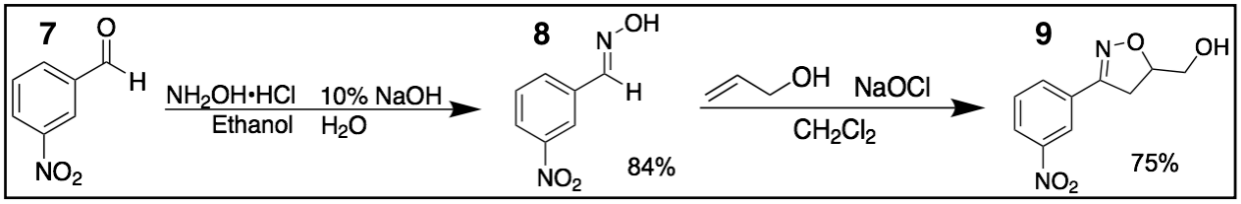
has a lot more impurities than **Spectrum 1.8**. This can be from the one-pot reaction and not extracting between steps.



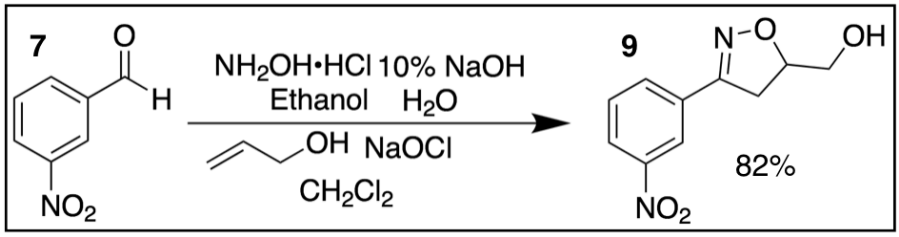
Scheme 1.3 Stepwise Synthesis of Isoxazoline starting with 3,4,5-Trimethoxybenzaldehyde



Scheme 1.4 One-Pot Reactions Starting with 3,4,5-Trimethoxbenzyaldehyde



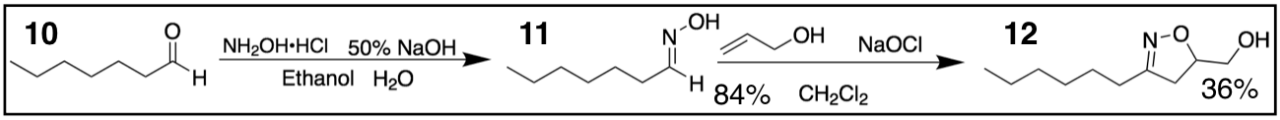
Scheme 1.5 Synthesis of Isoxazoline starting with 3-Nitrobenzaldehyde



Scheme 1.6 One-Pot Reactions Starting with 3-Nitrobenzaldehyde

Formation of Oxime Starting with Butyraldehyde, Heptaldehyde, and 3-Methylbutanal

When doing the same procedure as the aliphatic aldehydes (**10**), very little oxime (**11**) would form. Since very little oxime (**11**) formed, barely any or no isoxazoline (**12**) would form in the next step. Adjustments to the oxime procedure was made by using 50% sodium hydroxide instead of 10% sodium hydroxide. When this adjustment was done the reaction made more oxime (**11**) with less impurities and side reactions. When the next step was done, traces of isoxazoline (**12**) was produced but there was even more impurities and side reactions than isoxazoline. More research needs to be done to successfully find a reaction to make isoxazoline at a higher yield and then hopefully putting the two steps together to do a one-pot reaction. Below **Scheme 1.7** shows the most successful reaction scheme and percent yield of the product. Refer to **Spectrum 1.10** and **Spectrum 1.11** in the Appendix for ^{1}H NMR spectra. **Spectrum 1.10** oxime peak are at 0.85 ppm, 1.30 ppm, 2.15 ppm, and 7.38 ppm. In **Spectrum 1.11,** isoxazoline peaks are at 0.82 ppm, 1.26 ppm, 2.27 ppm, 2.96 ppm, 3.60 ppm, and 4.59 ppm. In both **Spectrum 1.10** and **Spectrum 1.11** there is a lot of impurities present. One distinguishable impurity is DCM at 5.28 ppm.



Scheme 1.7 Formation of Isoxazoline Starting with Heptaldehyde

Conclusions

This research found three one-pot synthesis reactions of isoxazolines. The first synthesis starts with anisaldehyde and produces 5-hydroxymethyl-3-(4-methoxyphenyl)-4,5-dihydroisoxazole. The second reaction starts with 3,4,5-trimethoxybenzaldehyde and produces 5-hydroxymethyl-3-(3,4,5-trimethoxyphenyl)-4,5-dihydroisoxazole. The third synthesis starts with 3-nitrobenzaldehyde and produces 5-hydroxymethyl-3-(3-nitrophenyl)-4,5-dihydroisoxazole. The reactants used in all these one-pot syntheses are hydroxylamine hydrochloride, 10% sodium hydroxide, ethanol, water, allyl alcohol, 3 % bleach solution, and dichloromethane. More research and experiments need to be done to find a one-pot synthesis to create 5-hydroxylmethyl-3-hexyl-4,5-dihydroisoxazole and other aliphatic isoxazolines and isoxazoles.

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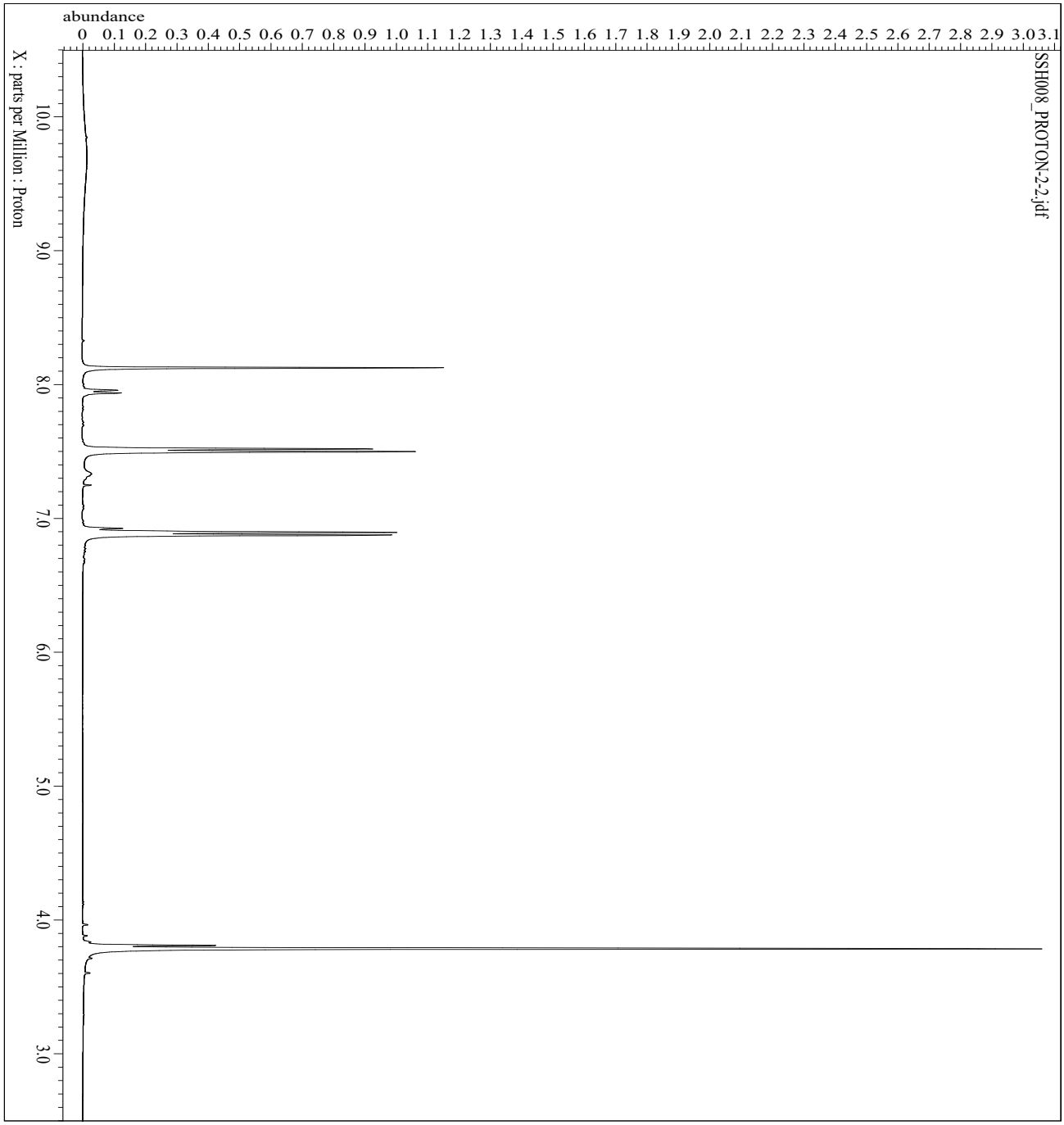
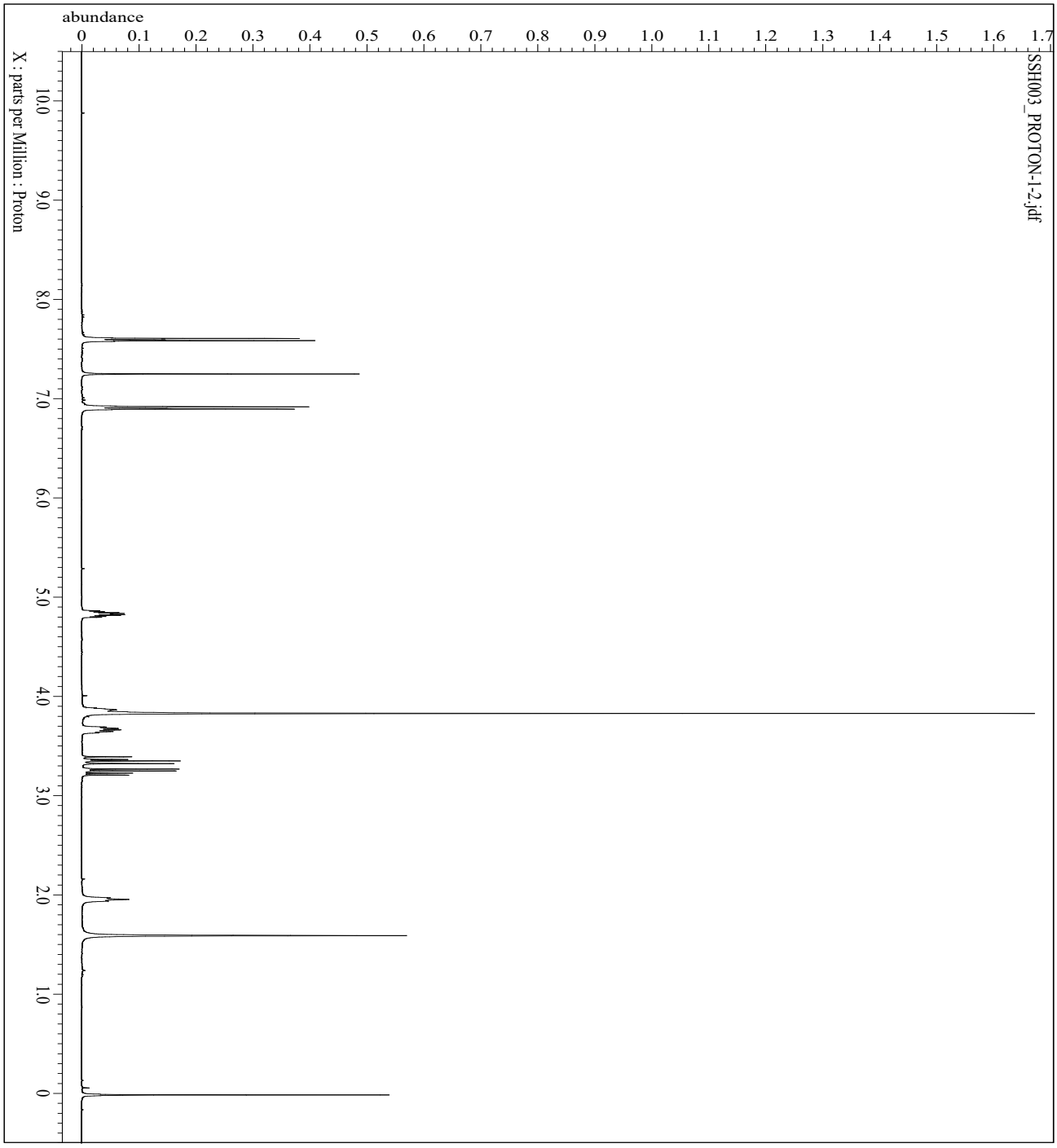
Appendix

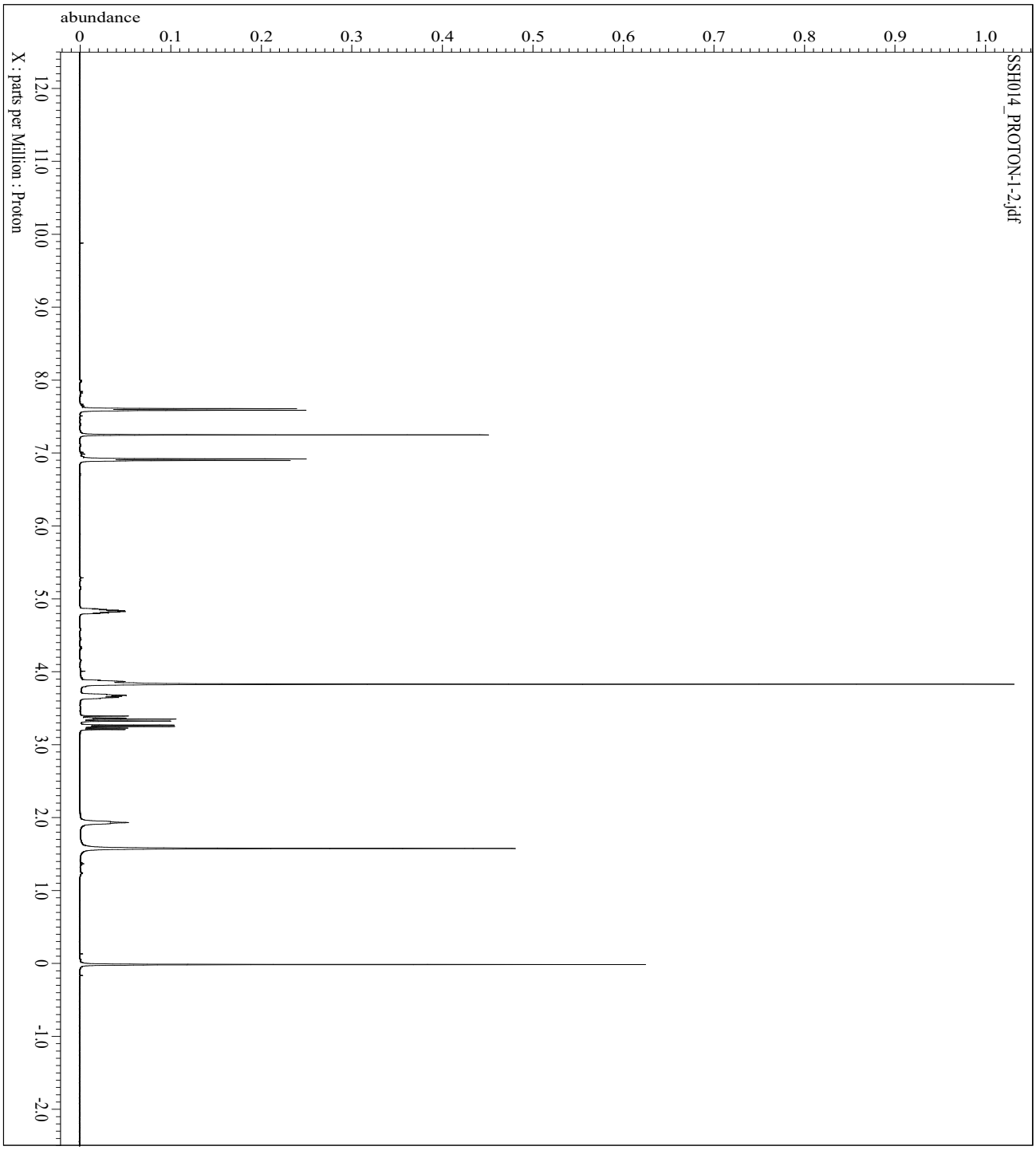
Spectrum 1.1 ^{1}H NMR Spectrum of 4-Methoxybenzaldoxime



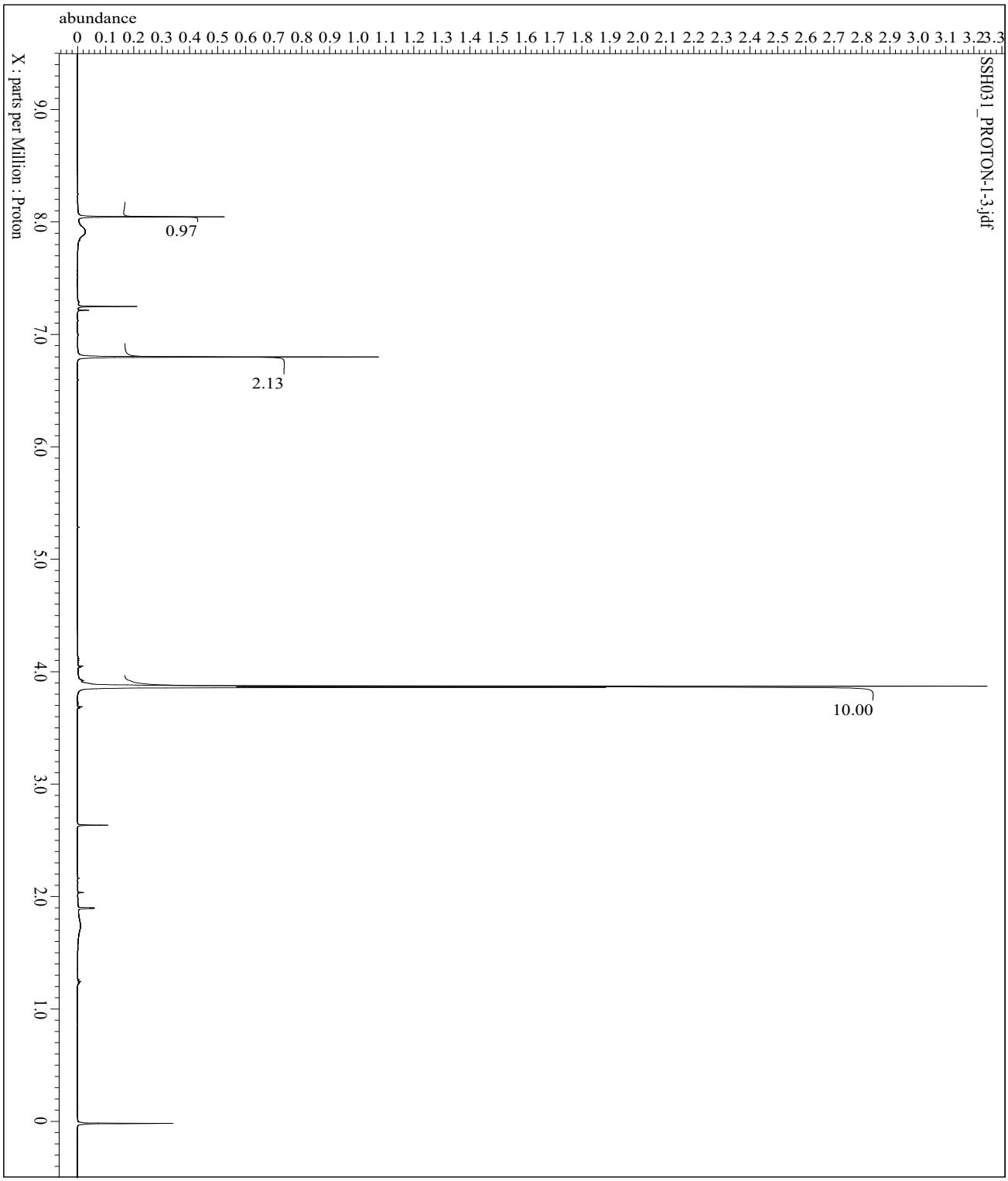
Spectrum 1.2 ^{1}H NMR Spectrum of 5-hydroxymethyl-3-(4-methoxyphenyl)-4,5-dihydroisoxazole



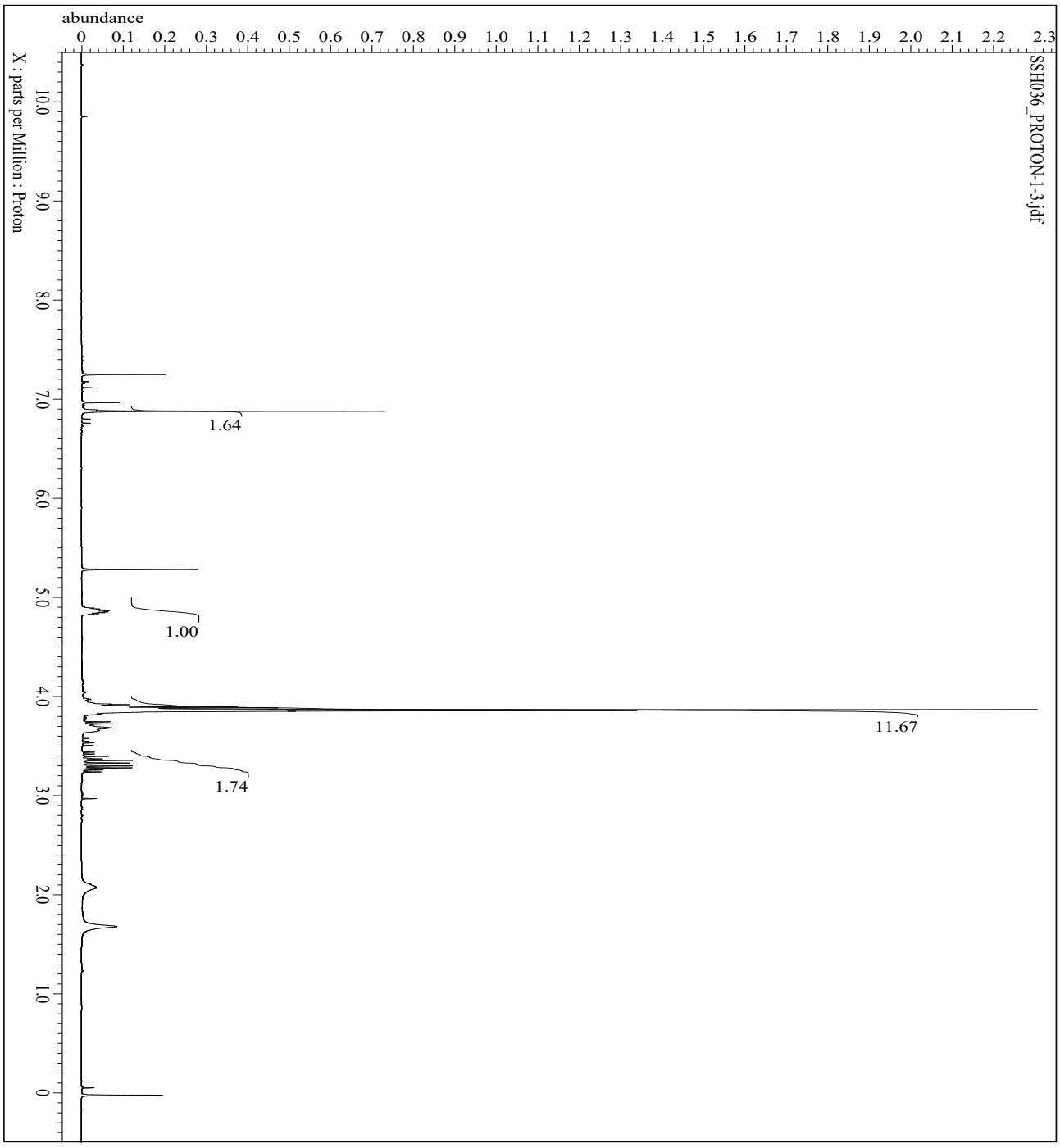
Spectrum 1.3 ^{1}H NMR Spectrum of One-Pot Synthesis of 5-hydroxymethyl-3-(4-methoxyphenyl)-4,5-dihydroisoxazole



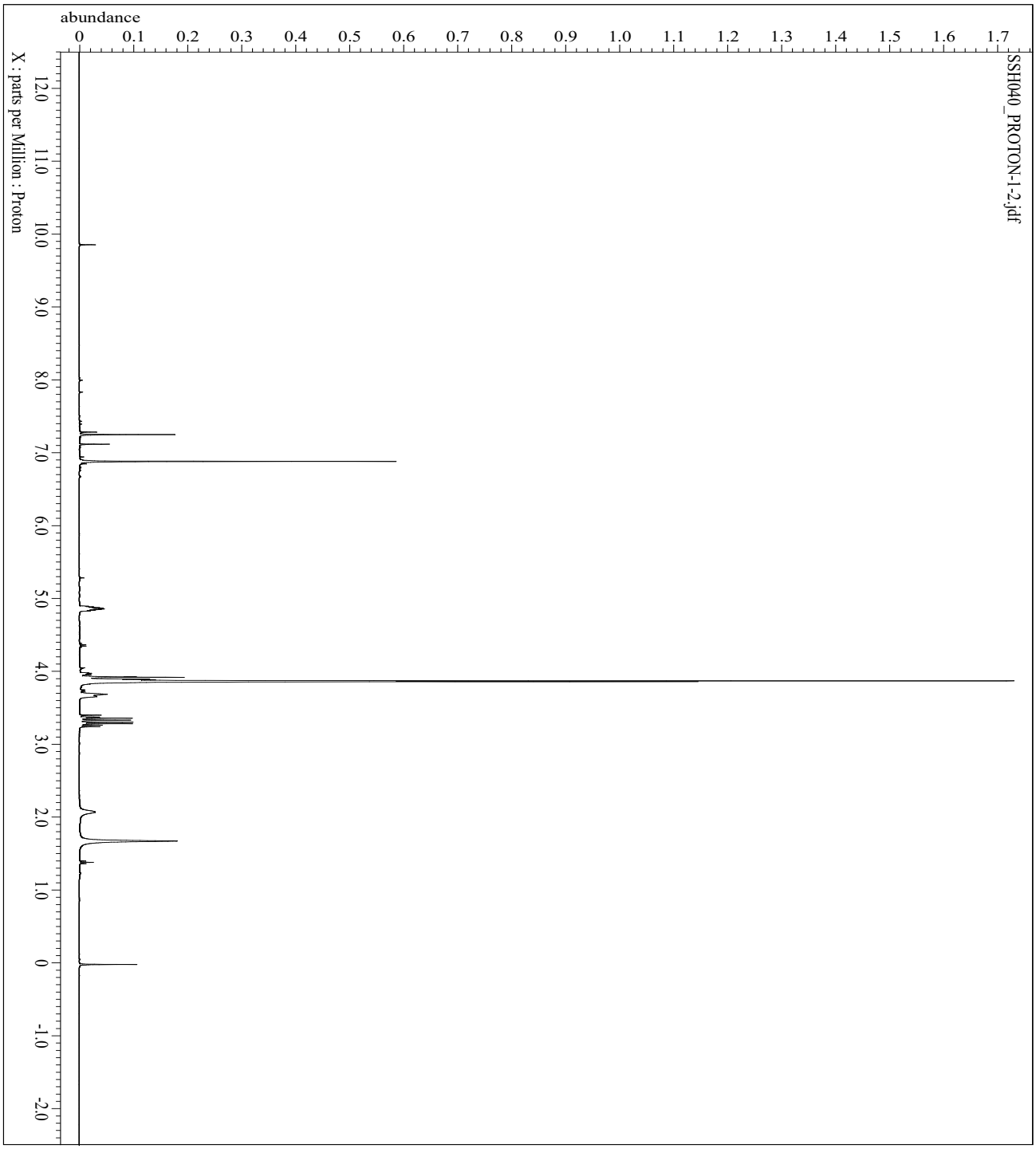
Spectrum 1.4 ^{1}H NMR Spectrum of 3,4,5-trimethoxybenzaldoxime



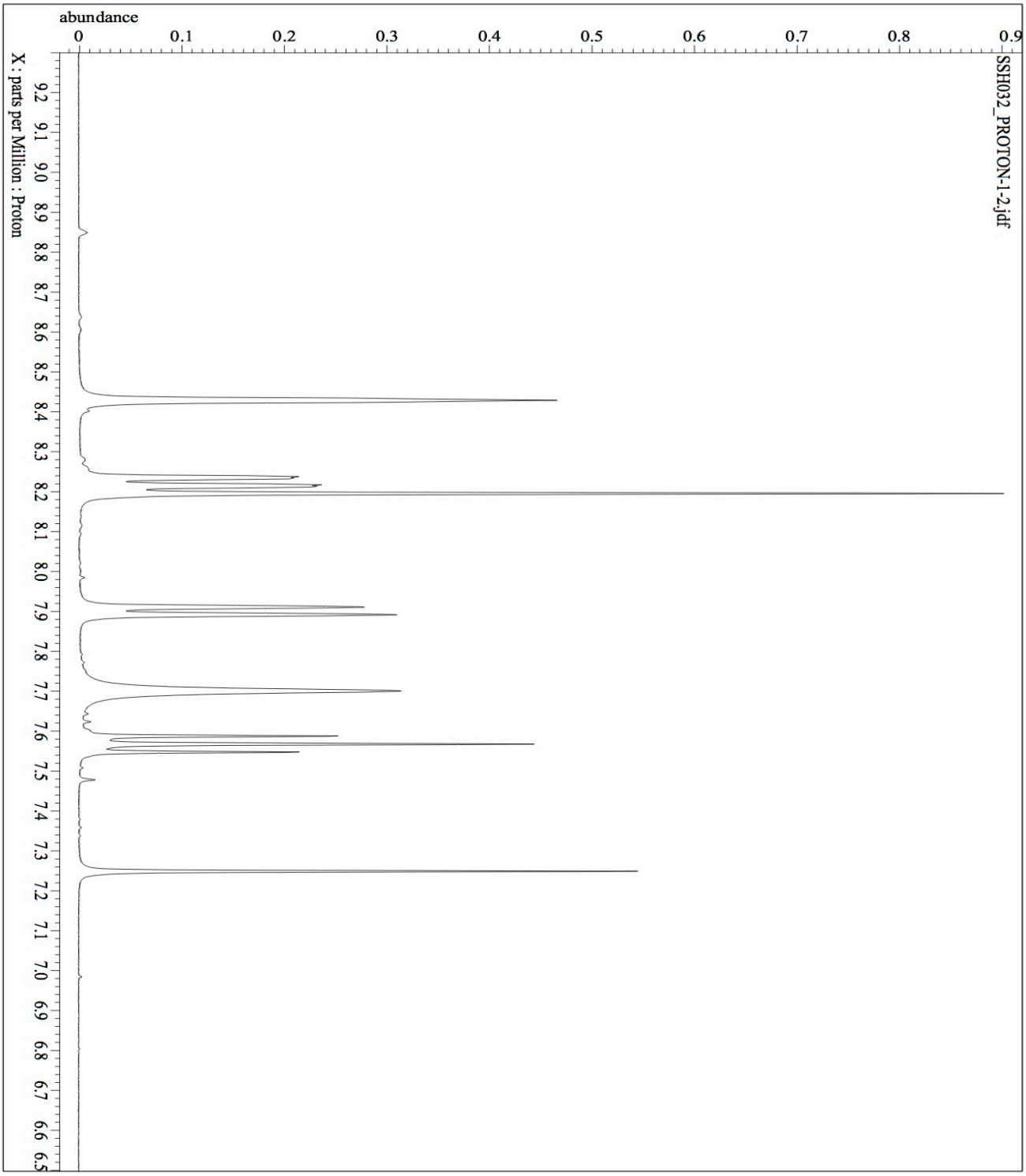
Spectrum 1.5 ^{1}H NMR Spectrum of 5-hydroxymethyl-3-(3,4,5-trimethoxyphenyl)-4,5-dihydroisoxazole



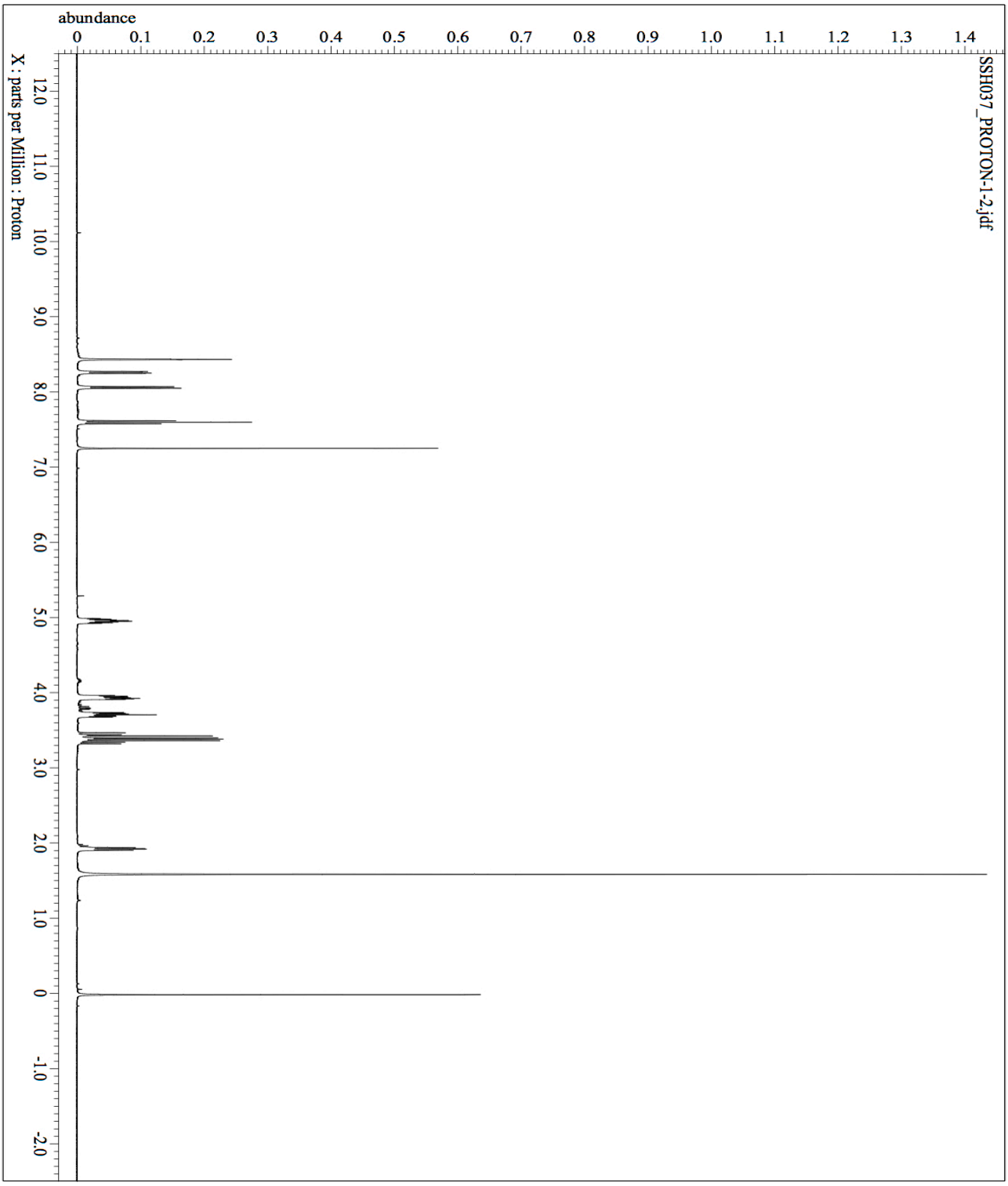
Spectrum 1.6 ^{1}H NMR Spectrum of One-Pot Synthesis of 5-hydroxymethyl-3-(3,4,5-trimethoxyphenyl)-4,5-dihydroisoxazole



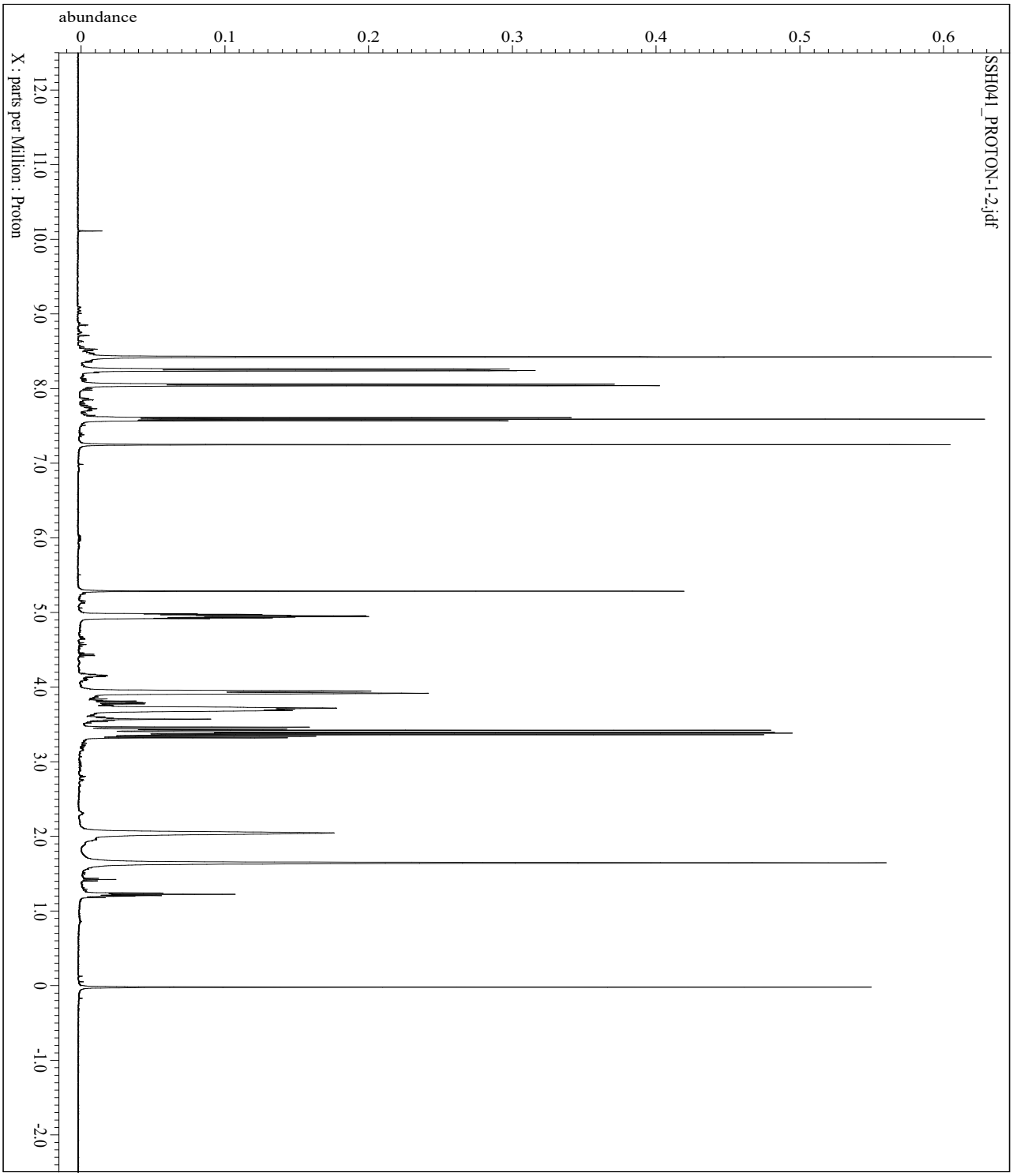
Spectrum 1.7 ^{1}H NMR Spectrum of 3-Nitrobenzaldoxime



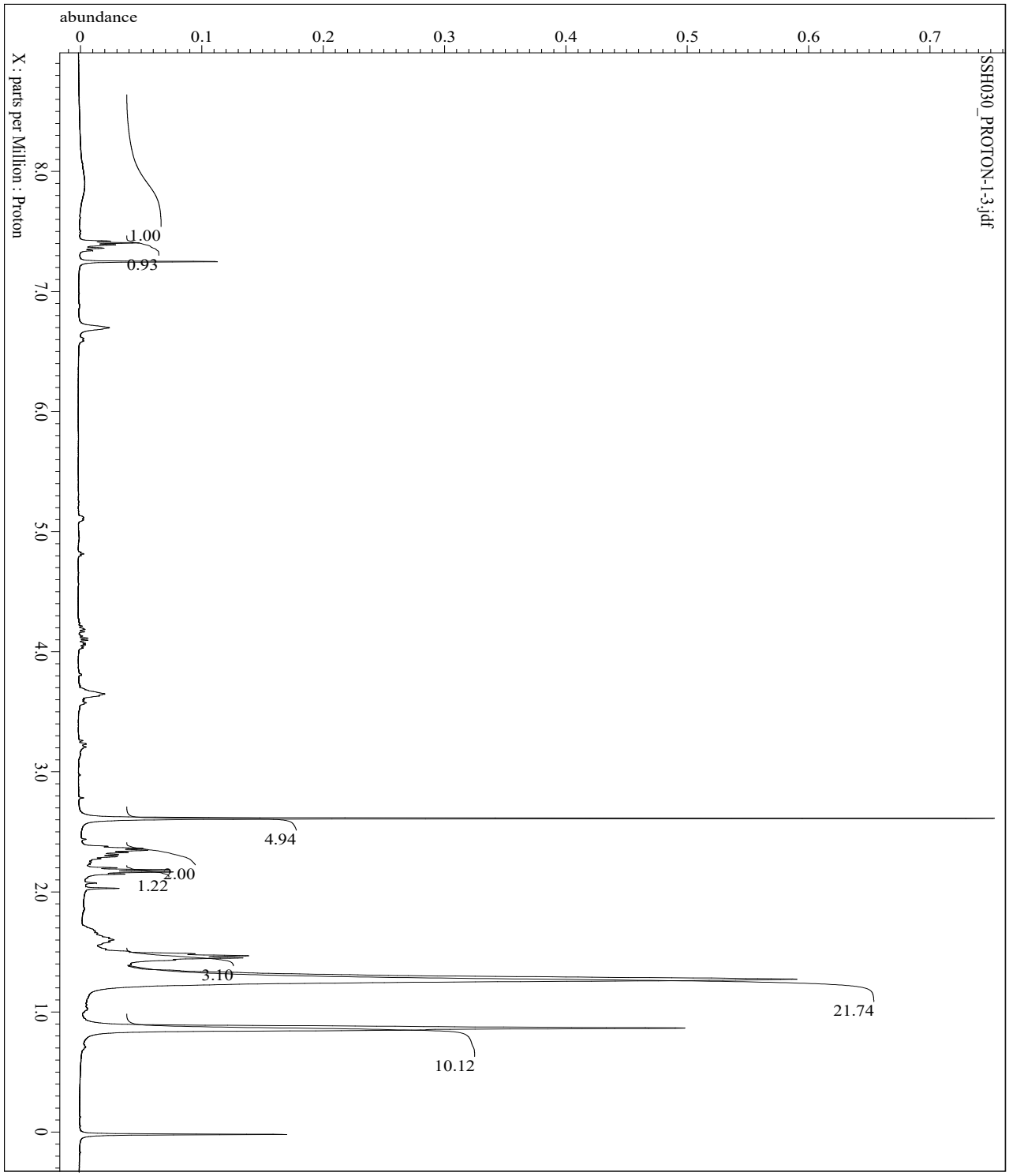
Spectrum 1.8 ^{1}H NMR Spectrum of 5-hydroxymethyl-3-(3-nitrophenyl)-4,5-dihydroisoxazole



Spectrum 1.9 ^{1}H NMR Spectrum of One-Pot Synthesis of 5-hydroxymethyl-3-(3-nitrophenyl)-4,5-dihydroisoxazole



Spectrum 1.10 ^{1}H NMR Spectrum of Heptaldoxime



Spectrum 1.11 ^{1}H NMR Spectrum of 5-hydroxylmethyl-3-hexyl-4,5-dihydroisoxazole